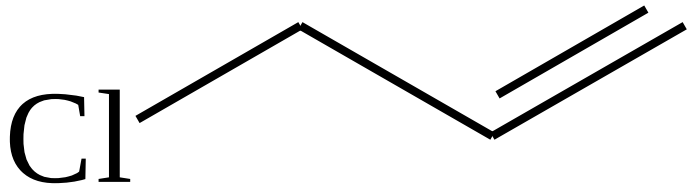
OEHHA

Allyl Chloride



Molecular Weight: 76.5

CAS Registry No.: 107-05-1

OEHHA

Listing History: Allyl Chloride

- Listed under Proposition 65 on January 1, 1990
- Based on a report U.S. EPA (U.S. EPA, 1987)
  - Limited animal data
  - Supporting evidence: mutagenicity, metabolism to epichlorohydrin, alkylation properties.
- Classified as a Group C carcinogen (U.S. EPA, 1990)

OEHHA

Reviews by Other Authoritative Bodies

- IARC
  - Group 3 carcinogen (IARC, 1985; 1987, 1999)
    - Inadequate evidence in experimental animals and humans
- NCI
  - “Suggestive evidence” (NCI, 1978)
    - Male and female B6C3F_1 mice, low incidence of rare forestomach neoplasms
    - No convincing evidence in rats of either sex

OEHHA

Human Carcinogenicity Data: Allyl Chloride

- Three occupational epidemiological studies: potential exposure to allyl chloride
  - Enterline *et al*., 1990: leukemia
  - Olsen *et al*., 1994
  - Tsai *et al*., 1996

None of these studies is informative about the carcinogenic effects of allyl chloride.

OEHHA

Forestomach Tumors B6C3F$_1$ Mice (NCI, 1978)

Tumor Site and Type		Dose, mg/kg$_{bw}$-day			
		vehicle	untreated	low	high
Males			0	175	199
Forestomach	Squamous Cell Carcinoma	0/20	0/20	2/46*	No survivors
Females			0	129	258
Forestomach	Squamous Cell Carcinoma	0/20	0/20	2/48	0/45
	Squamous Cell Papilloma	0/20	0/20	1/48	3/45

*Metastases and additional leiomyosarcoma of the forestomach.

Precancerous lesions of the forestomach in exposed animals of both sexes

Lung Adenomas in Strain A Mice (Theiss *et al*., 1979)

		Dose, mg/kg$_{bw}$			
Tumor Site and Type		control	low	mid	high
(Sexes combined)		0	0.65	1.6	3.2
Lung	Adenoma: Tumors per mouse	0.19 ± 0.10	0.6 ± 0.20	0.5 ± 0.27	0.60* ± 0.15

i.p. injection 3 times per week for 8 weeks

*Significant relative to control by one of two tests used by study authors: carcinogenic effect was considered “intermediate”.

OEHHA

Gavage Studies in Osborne-Mendel Rats (NCI, 1978)

		Dose, mg/kg_{bw}-day		
Tumor Site and Type		control	low	high
Males	No increased	0	57	77*
Females	tumor incidences	0	55	73*

78 w + 31-32 w observation

* Severe early mortality in both sexes in high-dose groups.

OEHHA

Skin Painting Studies in Mice (Van Duuren *et al*., 1979)

- Skin carcinogenicity:
  - 94 mg or 31 mg in acetone, 3 times per week (lifetime)
  - No tumors observed
- Initiation/promotion:
  - single application of 94 mg allyl chloride. After 14 d, 2.5 µg PMA 3 times per week
  - Skin papillomas in 7/30 mice, a significant ($p<0.025$) increase compared to PMA alone (9/120, 6/90)

Genotoxicity of Allyl Chloride

Species, strain	End-point	Result
Salmonella typhimurium		
100 (base substitution)	Reverse mutation	+
1535 (base substitution)	"	+
1538 (frame shift)	"	-
Escherischia coli		
Pol^+/Pol^-	DNA modification	+
WP_2, WP_2uvrA	Reverse mutation	+
Saccharomyces cerevisiae		
D4	Gene conversion	+
JD1	"	+
Aspergillus nidulans	Gene segregation	+
Rat liver - epithelial type cells, *in vitro*	Clastogenicity	-
HeLa cells, *in vitro*	Unscheduled DNA synthesis	+

OEHHA

Alkylating Activity

- Allyl chloride, a direct acting mutagen, binds to DNA *in vitro*
  - 3 guanine & 2 adenine adducts
- Metabolic activation enhances mutagenic activity
  - epichlorohydrin - DNA binding and DNA adducts *in vivo* & guanine adduct *in vitro*
  - glycidaldehyde - DNA adducts *in vivo & in vitro*

Structure-Activity Comparisons

- Several allyl compounds are known mutagens and/or carcinogens
- The proposed metabolites epichlorohydrin and glycidaldehyde are listed as causing cancer under Proposition 65

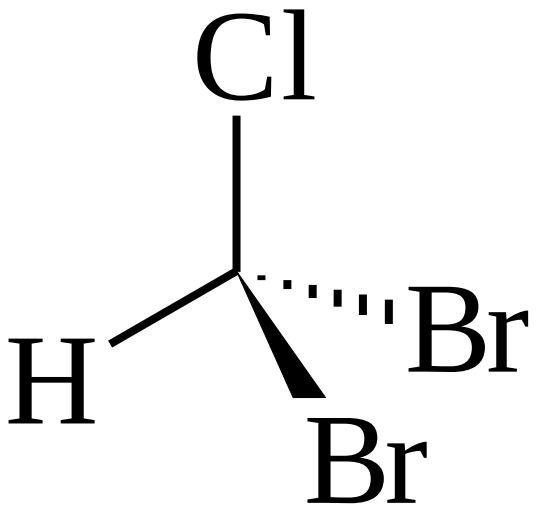
OEHHA

Summary: Allyl Chloride

- Oral exposure: rare squamous cell forestomach tumors in male and female mice
- The confidence in these findings is reduced by:
  - Severe toxicity and mortality, and resulting low power of the study
  - Marginal statistical significance of the results
- The confidence in these findings is increased by:
  - Precancerous lesions in the forestomach of both sexes of mice
  - Genotoxicity in a number of test systems
  - DNA alkylation
  - Structural relationship to other known mutagens and carcinogens
  - Apparent formation of known carcinogens as its metabolites

OEHHA

Chlorodibromomethane



Molecular Weight: 208.29

CAS Registry. No.: 124-48-1

OEHHA

Listing History: CDBM

- Listed under Proposition 65 on January 1, 1990
- Originally classified by U.S. EPA as a Group B2 carcinogen (U.S. EPA, 1989)
- Currently classified as a Group C carcinogen (U.S. EPA, 1997)

OEHHA

Reviews by Other Authoritative Bodies

- IARC (1991) - Group 3
  - *Inadequate evidence* - humans
  - *Limited evidence* - animals
- NTP (1985)
  - *Some evidence* in female $B6C3F_1$ mice
  - *Equivocal evidence* in male $B6C3F_1$ mice
  - *No evidence* in male or female F344/N rats

OEHHA

Carcinogenicity Data Available: CDBM

- Mouse chronic gavage studies (NTP, 1985)
  - Hepatocellular adenomas and carcinomas in female mice
  - Hepatocellular carcinomas in male mice
- Mouse chronic oral studies (Veronin *et al.,* 1987)
  - No increased tumor incidence

OEHHA

Carcinogenicity Data Available: CDBM

- Rat chronic gavage studies (NTP, 1985)
  - No increased tumor incidence
- Rat chronic dietary studies (Tobe *et al.*, 1982; as cited in U.S. EPA, 1997)
  - No increased tumor incidence

OEHHA

Mouse chronic gavage studies (NTP, 1985)

Tumor Site and Type		Dose Groups		
		Control	Low-dose	High-dose
Females				
Liver	Hepatocellular adenoma or carcinoma	6/50	10/49	19/50*
Males				
Liver	Hepatocellular carcinoma	10/50	-----**	19/50***
	Hepatocellular adenoma or carcinoma	23/50		27/50

* p = 0.01

** An accidental overdose caused the death of 35 low-dose males in week 58.

*** p = 0.03

OEHHA

Other Relevant Data: Genotoxicity of CDBM

Test System	Results
Salmonella typhimurium	+/-
Saccharomyces cerevisiae	+/-
Sister chromatid exchange	
Human lymphocytes in vitro, mouse bone marrow cells in vivo, rat erythroblastic leukemia cells	+
Chromosomal aberration	
Mouse lymphoma cells, Chinese hamster cells, rat bone marrow cells in vivo	+
Mouse bone marrow cells in vivo	-
***Micronucleus test**, mouse bone marrow cells in vivo*	-
***Rat liver unscheduled DNA synthesis test** in vivo*	-
***DNA strand break in rat kidney cells** in vivo*	-

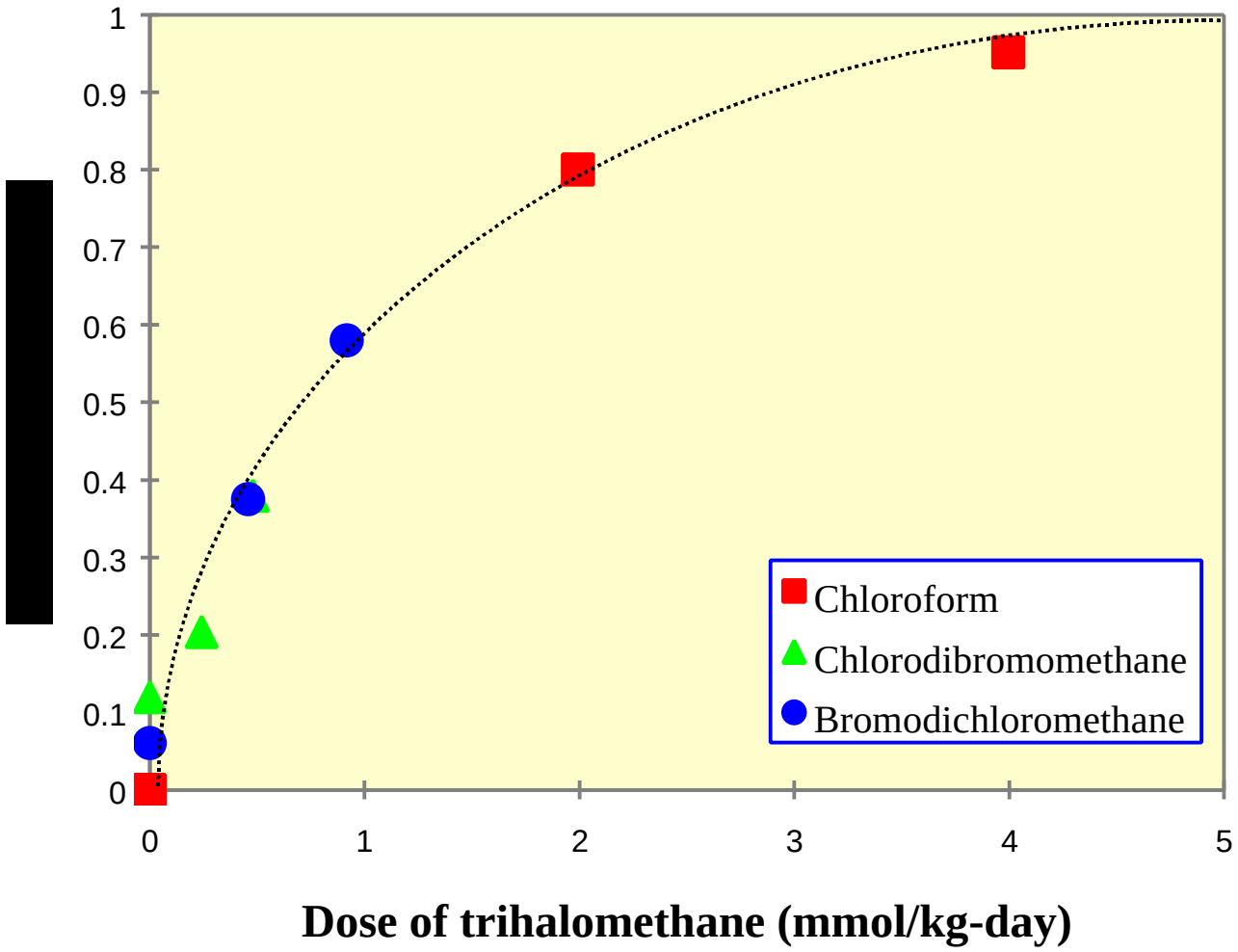
OEHHA

SAR with Other Trihalomethanes: Chloroform, dichlorobromomethane, and bromoform

- CDBM, chloroform and dichlorobromomethane cause liver tumors in mice
- Similar dose-response for liver tumor induction
- Mutagenicities of brominated trihalomethanes can be mediated by GST1-1. Similar mutation spectra (DeMarini *et al.,* 1997)

OEHHA

Dose-response of liver tumors with THMs

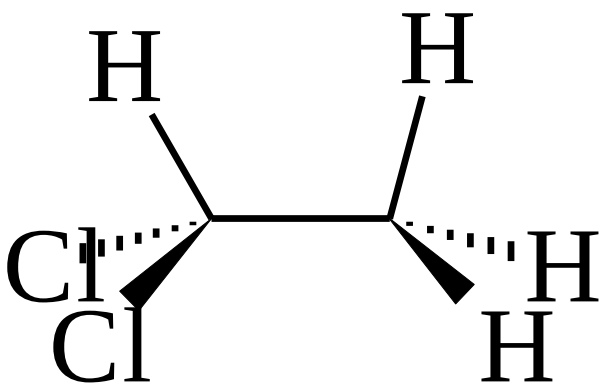


Summary: CDBM

- Liver tumors in mice
- Positive mutagenicity data
- Structural similarities with other carcinogenic trihalomethanes

OEHHA

1,1-Dichloroethane (1,1-DCA)



Molecular Weight: 98.96
CAS Registry No.: 75-34-31

OEHHA

Listing History: 1,1-DCA

- Listed under Proposition 65 on January 1, 1990
- Based on listing (B2) by US EPA, 1989 Health Effects Summary Tables
  - Based on NCI, 1978 bioassay
- US EPA Revised to Group C
  - Lack of evidence in humans
  - Limited evidence in rats and mice

OEHHA

Carcinogenicity Data Available: 1,1-DCA

- Humans
  - No evidence available
- Animals

  NCI (1978)
  - M/F B6C3F$_1$ mice, gavage, 78 wk (+13 wk obs.)
  - M/F Osborne-Mendel rats, gavage, 78 wk (+33 wk obs.)

OEHHA

NCI (1978)

Survival (%) at end of study

	Dose group		
	Control	Low	High
Mouse males	55	62	32
Mouse females	80	80	50
Rat males	5	4	8
Rat female	20	16	18

OEHHA

Tumors in B6C3F$_1$ Mice (NCI, 1978)

1,1-DCA by gavage in corn oil: 78 wk + 13 wk observation		**Dose Group**			
Tumor Site and Type		pooled controls	low	high	Trend
Males					
Liver	Hepatocellular Carcinoma*	6/72	8/48	8/32 (p=0.027)	p=0.016
Females					
Uterus	Endometrial stromal polyps*	0/79	0/47	4/46 (p=0.017)	p=0.005

* Statistically significant association ($p<0.05$) by survival analysis (Gold and Zeiger., 1997)

OEHHA

Tumors in Osborne-Mendel Rats (NCI, 1978)

1,1-DCA by gavage in corn oil: 78 wk + 33 wk observation		**Dose Group**			
Tumor Site and Type		pooled controls	low	high	
Males					
		No treatment-related tumors			
Females					Trend
Circulatory system	Hemangiosarcoma*	0/39	0/50	4/50 (p=0.09)	p=0.02
Mammary gland	Adenocarcinoma*	1/39	1/50	5/50	p=0.08

* Statistically significant association ($p<0.05$) by survival analysis (Gold and Zeiger, 1997)

OEHHA

Other Relevant Data

- Tumor promotion studies
  - 1,1-DCA did not exhibit initiating potential
  - 1,1-DCA was positive as a tumor promoter
- DNA binding studies
  - 1,1-DCA administered in vivo to rats and mice resulted in covalent binding to DNA and other macromolecules

OEHHA

Other Relevant Data

- Genotoxicity

Test System	Response
Reverse Mutation, *S. typhimurium*	-
Reverse Mutation, *S. typhimurium* (closed system)	+
Induction of mitotic segregation, haploids and non-disjuctional haploids; mitotic arrest, *Aspergillus nidulans*	+
Cell transformation assay, BALB/c-3T3	-
DNA-repair test, rat and mouse hepatocytes	+
Viral transformation assay, Syrian Hamster Embryo cells	+
Fluorometric assay of alkaline DNA unwinding, mouse *in vivo*	-

OEHHA

Structure-Activity Comparisons

- 1,2-DCA: NCI, 1978 (gavage)

	1,2-DCA	1,1-DCA
Male rats		
◆ Forestomach squamous cell carcinomas	✓	
◆ Circulatory system hemangiosarcomas	✓	✓ (females)
Female rats		
◆ Mammary adenocarcinomas	✓	✓
Male mice		
◆ Hepatocellular carcinoma	✓	✓
◆ Lung adenoma	✓	
Female mice		
◆ Endometrial stromal polyps	✓	✓
◆ Lung adenoma	✓	

- 1,2-DCA non-positive by other routes

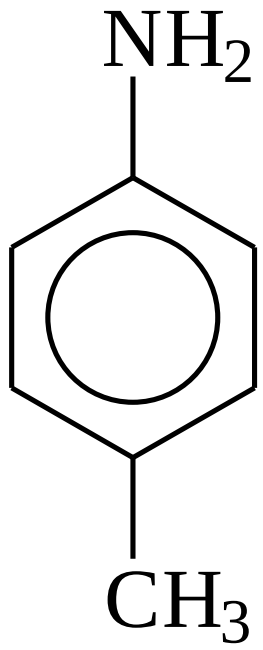
OEHHA

Summary: 1,1-DCA

- Carcinogenicity
  - Observations of increased tumor incidences in male mice (liver), female mice (uterus -benign), and female rats (circulatory system and mammary gland)
  - Problems with study quality: high doses, low survival
  - Low tumor incidences
- Other relevant data
  - Positive genotoxicity
  - Chemical structural analogies
  - Tumor promoting activity

OEHHA

p-Toluidine



Molecular Weight: 107.15

CAS Registry No.: 106-49-0

OEHHA

Listing History: *p*-Toluidine

- Listed under Proposition 65 on January 1, 1990
- Originally classified by U.S. EPA as a Group B2 carcinogen (U.S. EPA, 1986)
- Subsequently reclassified as a Group C carcinogen (U.S. EPA, 1988)

OEHHA

Reviews by Other Authoritative Bodies

- NIOSH
  - 1992 *Recommendations for Occupational Safety and Health, Compendium of Policy Documents and Statements*
  - “potential for cancer; tumors of the liver in animals”
  - “should be designated” as a potential occupational carcinogen

Reviews by Other Authoritative Bodes (cont.)

- U.S. FDA (1998, 1999)
  - Impurity in dye (D&C Violet No. 2) used in surgical sutures and tacks
  - “carcinogenic impurity that may be present”
  - “*p*-toluidine is a carcinogen in the mouse”

OEHHA

Carcinogenicity Data Available: *p*-Toluidine

- Mouse long-term diet studies (Weisburger *et al.*, 1978)
  - Increased hepatomas in male and female mice
- Male rat long-term diet study (Weisburger *et al.*, 1978)
  - No increased tumor incidence

Liver Tumors in CD-1 Mice (Weisburger , 1978)

Tumor Site and Type		Dose Groups		
		Control	Low-dose	High-dose
Males		3/18 (simult.)		
Liver	hepatoma	7/99 (pooled)	8/17*	9/18**
Females		0/20 (simult.)		
Liver	hepatoma	1/102 (pooled)	2/21	3/17***

* p = 0.0014 (vs. pooled controls)
** p = 0.038 (vs. simult. controls)
*** p = 0.009 (vs. pooled controls)

OEHHA

Other Relevant Data: *p*-Toluidine

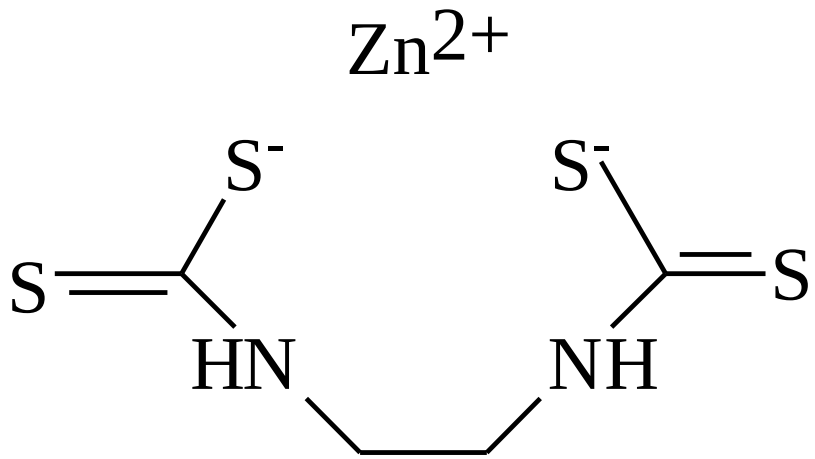
- Non-positive mutagenicity assays in *Salmonella* and *E. coli*
- Increased unscheduled DNA synthesis in rat hepatocytes (Thompson *et al.*, 1983)
- Decreased testicular DNA synthesis in mice following oral treatment (Seiler *et al.*, 1977)
- Hepatic DNA binding in rats (Brock *et al.*, 1990)

Summary: *p*-Toluidine

- NIOSH and U.S. FDA have designated *p*-toluidine as a carcinogen
- Scientific evidence supporting the designation was positive bioassays in male and female mice
- Other relevant data include positive DNA synthesis and hepatic DNA binding assays

OEHHA

Zineb



Molecular Weight: 275.7

CAS Registry No.: 12122-67-7

Listing History: Zineb

- Listed under Proposition 65 on January 1, 1990
- Originally classified by U.S. EPA as a Group B2 carcinogen (U.S. EPA, 1988)
- Entered into, then dropped from Special Review process
- Never re-classified

OEHHA

Reviews by Other Authoritative Bodies

- IARC (1976; 1987)
  - Group 3 carcinogen
    - insufficient evidence in animals
    - no human data

OEHHA

Carcinogenicity Data Available: Zineb

- Mouse sub-chronic oral studies (Chernov and Khitsenko, 1969)
  - Increased lung adenomas in C57BL mice
- Rat long-term oral studies (Mitsumori *et al.*, 1979)
  - Increased thyroid tumors in rats (primarily cystic adenomas)

OEHHA

Lung Tumors in Mice (Chernov & Khitsenko, 1969)

C57BL mice Lung adenomas	Dose (mg/kg_{bw}) 0	 1750	 3500
High-dose study	0/87		6/79*
Low-dose study	0/59	2/29	

Strain A mice Lung adenomas	Dose (mg/kg_{bw}) 0	 	 3500
High-dose study	30/97		35/101

* Significant increase relative to controls ($p < 0.05$, by Fisher's Exact test)

OEHHA

Thyroid tumors in rats (Mitsumori *et al.*, 1979)

- Rats (80/sex/group) treated with zineb in diet at 0, 40, 200, 1000, 5000 ppm for 130 weeks
- Increased thyroid tumors in males at 5000 ppm
  - 37.5% treated *vs*. 11.3% controls
  - primarily cystic adenomas
- Increased subcutaneous fibromas in males at 5000 ppm

OEHHA

Non-positive studies: Zineb

- Mouse oral studies (Innes *et al.*, 1969) - small; less-than-lifetime
- Mouse s.c. injection studies (NTIS, 1968) - small; less-than-lifetime
- Rat gavage and s.c. implant studies (Andrianova & Alekseev, 1970) - poor survival
- Rat oral studies (Blackwell-Smith *et al.*, 1953) - small study

Other Relevant Data: Zineb

Species, strain	Endpoint	Results	Reference
Salmonella typhimurium	Reverse mutation	– –	Croce *et al*., 1995 Franekic *et al*., 1994
Bacillus subtilis	DNA damage Mutation	+ +	Shiau *et al*., 1980 Felkner *et al*., 1981
Saccharomyces cerevisiae	Gene mutation Mitotic chromosome malsegregation	+ +	Franekic *et al*., 1994 Croce *et al*., 1995
Drosophila melanogaster	Genetic damage to somatic and germ cells Mutagenicity	+ –	Tripathy *et al*., 1988 Benes and Sram, 1969
Human peripheral blood lymphocytes	Increased chromosome aberrations	+	Pilinskaya, 1974 (cited in IARC, 1976)

Other Relevant Data: Zineb

- Structural similarity to other ethylene bisdithiocarbamate carcinogens
  (mancozeb, maneb, metiram)

- Metabolized / degraded to ethylene thiourea

Summary: Zineb

- Animal evidence includes benign lung tumors in mice and primarily benign thyroid tumors in rats
- Supporting evidence includes:
  - Some evidence of genotoxicity
  - Structural similarity to known carcinogens
  - Metabolism / degradation to ETU, a known carcinogen, with site concordance